EMF

THE ROCKEFELLER UNIVERSITY

pro bono humani generis

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Dr. Tom Langfitt
The Pew Trust
215:419-6678 ✓3/5/97

Dear Tom:

Some background -- you can locate Larry Ellison easily in reports in Business Week, Fortune, etc. in re Oracle Corporation.

The best contact is his chief of staff:

Rick Moore
Senior Vice President &
Chief of Staff
Office of the Chairman & CEO
Oracle Corporation
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Draft prospectus, Ellison Medical Foundation

(J. Lederberg, Sept. 1996)

Gerobiology

Higher organisms, including the human, traverse an eternal cycle of birth, development, maturation, senescence and death.

The latter part of this cycle is "aging", and is all too often associated with debilitation, pain and psychic distress, not to mention economic loss. Civilization, through improved hygiene and personal security, has brought us some deferral of death but its paradoxical companion is a greater exposure to the interval of senescence. As the human species brings its intelligence to bear on the humane reordering of its own condition, it is a natural desire to defer death and mitigate senescence, i.e. to counter aging.

Aging is intertwined with the entire developmental cycle; but the progression from maturity to senescence is not always inexorable. Even the metamorphosis from tadpole to frog is under

hormonal control; in plant life, we see both evanescent annuals, and conifers that survive for millenia. The natural history of the 100- or 1000- fold range of life spans of vertebrate animals, from weeks to centuries, is the most compelling clue that the tempo of aging is under biological control, and in principle that it is amenable to fundamental re-engineering.

There is probably no single "cause" of aging, as every aspect of normal development, and so many chronic pathologies are time- dependent processes. We can pinpoint diseases of specific organ systems, notable the heart, the brain, immune system, and cancers and observe how prophylactic and therapeutic interventions would prolong life, well-being and good health.

We would then be left with further questions:
1) To what extent would deepseated cellular and metabolic processes contribute to the march of these end-organ pathologies?
2) If these were mitigated, one by one, how would life span still be limited by more generalized aging of cells and tissues?
3) What are the cell-structural and molecular loci of that intrinsic aging?

A parallel domain, that offers at least some provocative metaphors for gerobiology is aging that relates to psychic and psychosocial function: how the accumulation of knowledge, experience, and insult leads to wisdom or to irascibility, rigidity and depression.

We have then to consider the clinical, organismic, cell-biological and molecular levels of enquiry, relating to the 3 questions above.

Cell and tissue aging might be classified as consequences of
a) intrinsic developmental programming -- ex.: closure of epiphyses
involution of thymus; depletion of oocytes
b) side effects of defensive systems -- ex.: apoptosis; autoimmunity
calcification of tendons
c) metabolic or physiological accidents -- ex.:
scars, emboli, protein cross-links, viral invasions, DNA
lesions (chromosomal or mitochondrial)

In phylogeny, natural selection has favored reproductive efficiency and may be indifferent to, even at cross-purposes, with life span beyond the ages of fecundity.

Gerobiology, the biological study of aging, then offers challenges to every discipline. Molecular biology has surfaced some striking discoveries, like the recent isolation of the gene for Werner's Syndrome (premature aging) and the elucidation of telomeres -- chromosome caps that are self-renewing in the germline but not in many somatic tissues. There are also exciting new clues to the genetic etiology of Alzheimer's Disease; the regulation of apoptosis (esp. wrt cancer), susceptibility to atherosclerosis. And there are epidemiological leads on hormonal interventions for the neuro-immune axis.

It is the goal of the EMF to promote still more innovative interdisciplinary convergence on problems of aging. While substantial federal funding, over $400 MM in the NIA budget, is dedicated to aging research, only ___% addresses gerobiology, and it suffices to provide completed funding for only __(about 12)% of the proposals judged excellent by peer review. In this stringent climate, the grants process is notorious for its aversion to risk; and this has been internalized in the timidity of researchers in submitting only those proposals which can evade any criticism; and indeed many of them reflect work fairly far down its own cycle of looming senescence. The EMF will therefore be especially receptive to proposals from established workers in *other* fields who are entering gerobiological research for the first time, as well as to any which show other evidence both of competence and of vulnerability to the traditional funding paradigms.

modus operandi

The initial grants program of the EMF will embrace a funding commitment of $2 MM per year, in the form of grants that may extend over a period up to 4 years. Individual grants may be in the range of $100,000 to 300,000 per annum , and will be awarded after review by a distinguished scientific advisory board.

{commitments of $8 MM per year, for next 5 years, == 40MM} {first year outlay: $2mm; second 2+2 =$4MM, third year 2+2+2 =$6MM etc. at equilibrium, $8MM per year.}

plus additional funds, for conferences and publications

HOPED-FOR TIMETABLE

Announcement: March 1 1997
Organize Advisory Board
Disseminate RFP's May 1 1997
Deadline for submission: < Sep 15 1997
allow cycling for revised info from grantees
& allow time for review
Announce Awards: Feb 1 1998 *
Begin payout: Jun 1 1998 ff

*a date just within reasonable schedule for
recruiting post-docs for following academic year

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On above timetable, operational role for an alliance could be deferred to not later than about Sept. 1 1997, when the proposals would be coming in and have to be processed. Obviously the earlier the better to clear matters of doctrine etc.

This is Larry's first major philanthropy, and his way to familiarize himself with the process. He is one of the most incisive intellects I know. It is one measure of the man that he spent two weeks in my lab (summer 1994) as his holiday, as assistant to my 20-year old daughter, just to get hands on experience with molecular biology!

He is also deeply interested in role of computers and communications technology in education , and will be putting a lot of thought and money into that sphere.

Josh